4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2014-N-0129]

Application of Physiologically-Based Pharmacokinetic Modeling to Support Dose Selection; Notice of Public Workshop; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing a public workshop entitled “Application of Physiologically-Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection.” The purpose of the workshop is to obtain input on scientific approaches for the conduct and assessment of physiologically-based pharmacokinetic (PBPK) modeling within the framework of drug development and regulatory decisionmaking. The input from the workshop may be used to refine FDA’s thinking on the various applications of PBPK. Preliminary elements of a draft concept paper will be presented to facilitate discussion at this public workshop.

DATES: The workshop will be held on March 10, 2014, from 8:30 a.m. to 4:30 p.m. Individuals who wish to attend the workshop must register by February 24, 2014. Please submit either electronic or written comments by April 10, 2014, to receive consideration.

ADDRESSES: The public workshop will be held at FDA’s White Oak Campus, 10903 New Hampshire Ave., Bldg. 2, rm. 2047, Silver Spring, MD 20993. Participants must enter through Building 1 and undergo security screening. For parking and security information, please visit

http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm.

Please submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Identify all comments with the corresponding docket number found in brackets in the heading of this notice. A transcript of the workshop will be available for review at the Division of Dockets Management and at http://www.regulations.gov approximately 30 days after the public workshop (see section VI of SUPPLEMENTARY INFORMATION).

FOR FURTHER INFORMATION CONTACT: Ping Zhao, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg.51, Rm. 3182, Silver Spring, MD 20993, 301–796–3774, FAX: 301–847-8720, email: ping.zhao@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112–144). Title I of FDASIA reauthorizes the Prescription Drug User Fee Act (PDUFA) and provides FDA with the user fee resources necessary to maintain an efficient review process for human drug and biological products. The reauthorization of PDUFA includes performance goals and procedures for the Agency that represent FDA's commitments during fiscal years 2013–2017. These commitments are fully described in the document entitled ''PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017'' ("PDUFA Goals Letter"), which is available at

http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf. Section IX of the PDUFA Goals Letter, entitled ''Enhancing Regulatory Science and Expediting Drug Development," includes provisions to promote innovation through enhanced communication between FDA and sponsors during drug development. As part of this enhanced communication, FDA made a commitment to hold a public workshop to: (1) Engage stakeholders in a discussion of current and emerging scientific approaches and applications for the conduct of PBPK modeling and simulations and (2) to facilitate stakeholder input regarding the utility of PBPK during drug development and regulatory review. The public workshop announced by this document will fulfill this commitment.

PBPK modeling is a mathematical modeling technique for predicting drug behavior in humans. A PBPK model takes information about a drug's physical, chemical, and other properties, as well as information about processes in the body, and turns them into mathematical equations to predict what will happen when a patient takes the medication. Consequently, PBPK models may be a useful platform in risk assessment during drug development.

II. Purpose and Scope of the Workshop

The objectives of the workshop are to:

1. Share and discuss best practices in the use of PBPK to inform dose selection in specific patient populations, such as patients with renal or hepatic impairment, pediatric patients, elderly patients, and patients with genetic variation,

2. Discuss the current state of knowledge and share current FDA experience regarding important criteria for evaluating the adequacy of PBPK models for intended uses, as well as criteria for considering modeling results when making regulatory decisions,

3. Obtain input on specific issues identified by FDA on the conduct of PBPK analysis.

Since the 1970s PBPK modeling and simulation has been routinely used in toxicology to assess the risk of environmental toxins that cannot be safely studied in humans. In the past decade, PBPK models have increasingly been applied to complex drug development issues that cannot be evaluated in a clinical trial or to issues that can be reliably assessed in silico, thereby minimizing the need for costly clinical trials. These types of applications of PBPK are submitted to FDA for regulatory review. As a result, FDA is looking to adopt a rigorous approach to the review of PBPK submissions and the conduct of de novo PBPK analysis to support regulatory review. FDA also wishes to be transparent regarding its evidentiary standards and how it weighs the evidence of a PBPK simulation in arriving at a decision or regulatory action.

The public workshop will focus on the use of PBPK models for assessing the effect of various intrinsic and extrinsic factors in order to inform dose optimization. FDA acknowledges, however, that PBPK can be used to support decision making through the entire life cycle of drug development, including preclinical and clinical evaluations.

The input from the workshop may be used to refine FDA's thinking on use of PBPK in determining proper dosage and may lead to the development of a draft guidance for industry. There is currently no FDA guidance on this topic. Specifically, this guidance would describe FDA's view of criteria considered important when evaluating the strength and quality of evidence provided by a PBPK analysis.

FDA will also be preparing a concept paper that will propose best practices and principles for the use of PBPK modeling in drug development and regulatory review. Preliminary elements of this document will be presented at the public workshop by FDA to elicit comments and

facilitate discussion. The paper will incorporate the workshop outcomes, then the public will be invited to comment through a public docket.

III. Scope of Public Input Requested

FDA seeks input on a range of topics related to the conduct of PBPK modeling and simulation by pharmaceutical industries and by FDA and on the interpretation and use of simulations when evaluating risk in the regulation of pharmaceutical products. These include:

1. Predictive performance of PBPK models for a specific aim
2. Identification of knowledge gaps in the specific application of PBPK simulation to replace a clinical trial:
    a. Criteria for the adequacy of a PBPK model for a specific aim
    b. Biological plausibility and predictive performance
    c. Model validation and statistical considerations
3. Presentation of simulations in approved product labeling (labeling):
    a. When should PBPK simulations be included in drug labeling?
    b. What is the best format for presenting PBPK simulations in different sections of the labeling?
    c. How should uncertainty in simulations be presented in the labeling?

IV. Attendance and Registration

The FDA Conference Center at the White Oak Campus is a Federal facility with security screening and limited seating. Individuals who wish to attend the public workshop must register on or before February 24, 2014, by visiting https://www.surveymonkey.com/s/MW5WZDW and

contacting Ping Zhao (see FOR FURTHER INFORMATION CONTACT). Early registration is recommended. Registration is free and will be on a first-come, first-served basis. However, FDA may limit the number of participants from each organization based on space limitations. Onsite registration on the day of the workshop will be based on space availability.

During the workshop, time will be designated for questions and answers throughout the day and for general comments and questions from the audience following the panel discussions.

In this Federal Register document, FDA has included specific issues that will be addressed by the panel. If you wish to address one or more of these issues in your presentation, please indicate this at the time you register so that FDA can consider that in organizing the presentations. FDA will do its best to accommodate requests to speak and will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin. An agenda will be available approximately 2 weeks before the workshop at http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm (select this workshop meeting from the events list).

If you need special accommodations because of a disability, please contact Ping Zhao (see FOR FURTHER INFORMATION CONTACT) at least 7 days before the workshop.

A live webcast of this workshop will be viewable at https://collaboration.fda.gov/pbpk/ on the day of the workshop. A video record of the workshop will be available at the same web address for 1 year.

V. Comments

Regardless of attendance at the public workshop, interested persons may submit written or electronic comments to the Division of Dockets Management (see ADDRESSES). It is only

necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this notice. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

VI. Transcripts

Transcripts of the workshop will be available for review at the Division of Dockets Management (see ADDRESSES) and at http://www.regulations.gov approximately 30 days after the workshop. A transcript will also be made available in either hard copy or on CD–ROM upon submission of a Freedom of Information request. Send requests to Division of Freedom of Information (ELEM–1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

Dated: February 5, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-02883 Filed 02/10/2014 at 8:45 am; Publication Date: 02/11/2014]